REMARKS

Claims 1-32 were present in the application as filed. A Preliminary Amendment was filed concurrently with the application amending paragraph 1 of the specification to provide updated cross-reference to related applications information. An Amendment filed on December 11, 2003 provided a substitute Abstract. An Office Action with an Election/Restriction Requirement was mailed on December 13, 2005. In a Response filed on January 11, 2006, Applicants elected the invention of Group I (Claims 1-23, 32) drawn to a process of making compounds of formula IA and/or IB employing microorganisms selected from genera of *Stemphylium*, *Gliocladium*, etc.

A new Non-Final Office Action was mailed on March 29, 2006 rejecting claims 1-2, 25-32 and withdrawing from consideration claims 3-24. The Office Action is addressed below. Claims 1-16 and 18 have been amended. The claims now pending in the application are: 1-32.

ELECTION/RESTRICTION REQUIREMENT

The prior Office Action (December 13, 2005 Office Acton) imposed restriction between claims of Group I (claims 1-23, 32) drawn to a process of making formula IA or IB employing microorganisms selected from genera of *Stemphylium*, *Gliocladium*, etc., and claims of Group II (claims 24-31) drawn to a process of making formula IA or IB employing *Cunninghamella bainieria.*

Applicants, in January 11, 2006 Response, elected the invention of Group I (claims 1-23, 32) drawn to a process of making compounds of formula IA and/or IB employing microorganisms selected from genera of *Stemphylium*, *Gliocladium*, etc. An election of species requirement was also made and Applicants elected the microorganism species of *Stemphylium consortiale*, where the process involves incubating that is carried out at a temperature of 29 °C, pH of 7, for a period of 168 hours (7 days), and prior to the

incubating, the microorganism is subjected to multi-stage liquid culture induction. Claims that read on the species were identified by Applicants as claims 1, 2, 17-23, and 32.

However, in the March 29, 2006 Office Action, the Examiner stated that claim 2 and claims 1, 25-32 reading on claim 2 are to be prosecuted, while claims 3-24 are being withdrawn from consideration. Applicants respectfully assert that such claim assessment appears to be erroneous.

The Examiner and Applicants appear to agree that claims 1, 2, and 32 are within Group I (claims 1-23, 32) and encompass elected species. The Examiner and Applicants also appear to agree that claims 3-16 do not fall within the scope of elected species. However, Examiner's decision to withdraw from consideration claims 17-23 appears to be erroneous. Claims 17-23 variably depend on claim 1 and they all encompass the elected species embodiment. Further, the Examiner stated that claims 25-31 are to be examined and this appears to be in error since claims 24-31 are non-elected claims of Group II. Applicants believe that the present disagreement regarding claim assessment is a result of an inadvertent error on Examiner's part and appropriate correction is respectfully requested.

NEW MATTER REJECTION

The Examiner asserted that Applicants' intention of election to include pH 7 as a particular limitation of operating conditions constitutes new matter since Example 2 (providing operating conditions for Example 4) specifies pH of 5 rather than 7. However, Applicants direct the Examiner's attention to Table 2 of the specification where it is stated that *Stemphylium consortiale* was utilized at pH 7. Therefore, Applicants respectfully assert that specifying pH value of 7 was not new matter.

35 U.S.C. §112, FIRST PARAGRAPH REJECTION

The Examiner rejected claims 1-2, and 25-32 under 35 USC § 112, first paragraph, for alleged lack of description or enablement for all mutants or selectants of the microorganisms embraced by the claims.

Without acceding to the propriety of this rejection, and for the purposes of expediting prosecution of the application, Applicants hereby amend claims 1-16 to recite species of microorganisms exemplified in the specification. Applicants reserve their right to pursue the original scope of the amended claims in one or more continuation applications.

35 U.S.C. §103(a) REJECTION

The Examiner rejected claims 1-2, and 25-32 under 35 USC § 103(a) as allegedly being unpatentable over Azerad et al. (WO 99/47693) in view of Humphrey et al. (US 3,419,469), Herr at al. (US 3,649,453), Charpentier et al. (US 3,966,553), Goldberg et al. (US 4,564,594), Page et al. (US 5,032,513) or Witholt et al. (US 5,135,859) further in view of Umezawa et al (CA 84:178218). This rejection is respectfully traversed.

Azerad et al. disclose the preparation of fexofenadine from terfenadine in a bioconversion process using *Absidia corymbifera* LCP 63-1800 or *Streptomyces platensis* NRRL 2364 strain; *Aspergillus ochraceus* is also disclosed on page 12 of Azerad et al. Since the pending do not call for the use of a *Streptomyces* species, an *Aspergillus* species, or an *Absidia* species, they cannot be anticipated by Azerad et al.

Humphrey et al. discloses a process for the preparation of carboxylic acids by the fermentation of hydrocarbons in an anion exchange resin using *Micrococcus, Corynebacterium, Nocardia, Pseudomonas, Mycobacterium, Streptomyces, Aspergillus,* or *Acetobacter*. The hydrocarbons utilized in this process are those that

will be consumed nutritionally as a carbon source by the microbes, such as methyl substituted benzene, xylene, and naphthalene.

Herr et al. discloses a method for the introduction of oxygen into specific positions of 1-aminoadamantanes using *Sporotrichum sulfurescens, Rhizopus arrhizus,* or *Curvularia luanta.*

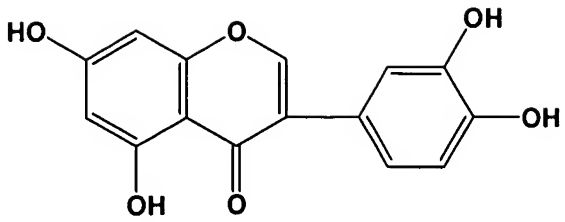
Charpentier et al. discloses a process for manufacturing citric acid by aerobic culture of yeast strains *Torulopis Candida,*or *Rhodotrula* in a medium containing at least one n-paraffin as a carbon source.

Goldberg et al. discloses a fermentation process for producing carboxylic acids, particularly fumaric acid, succinic acid, malic acid, and lactic acid, as metabolic by-products of the natural metabolism of certain *Rhizopus* species.

Page et al. discloses a process for the preparation of gamma and delta lactones from carboxylic acids with *Mucor* species. These reactions consume the simple carboxylic acid specified and are not oxidative conversions for the production of carboxylic acids.

Witholt et al. discloses a process for producing polyester biopolymers using *Pseudomonas olevorans*. The polymers are produced as by-products of the organism's natural metabolic consumption of simple hydrocarbons, especially linear paraffins containing 6-12 carbons.

Umezawa et al., according to the English language abstract provided by the Examiner, is directed to methods of making orobole by use of microorganisms of genera of *Stemphylium*, *Streptomyces*, and *Aspergillus*. According to the abstract, the structure of orobole is:



Thus, orobole is structurally very different from the products of the claimed invention. In particular, it should be noted that orobole lacks any carboxylic acid or ester functional groups that must be present in the claimed products due to definition of claimed R^3 group.

A proper *prima facie* showing of obviousness requires the U.S. Patent and Trademark Office ("PTO") to satisfy 3 requirements. First, the prior art relied upon, coupled with knowledge generally available to one of ordinary skill in the art, must contain some suggestion which would have motivated the skilled artisan to combine references. See In re Fine, 837 F.2d 1071, 1074,5 u.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the PTO must show that, at the time the invention was made, the proposed modification had a reasonable expectation of success. See Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the combination of references must teach or suggest each and every limitation of the claimed invention. See In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496. (CCPA 1970).

Application of these standards to the present invention clearly demonstrates the lack of even a *prima facie* case of obviousness. Although Azerad et al. discloses the preparation of fexofenadine from terfenadine in a bioconversion process using *Absidia* or *Streptomyces,* there is no suggestion in this reference or those it is cited in combination with that fexofenadine can be produced with the claimed microorganisms from terfenadine. All secondary references use very different microorganisms to effect very different reactions than Azerad et al. In view of these distinctions, one of ordinary skill in the art would have no motivation to combine the teachings of the secondary references with those of Azerad et al.

With respect to the secondary references, it should be recognized that neither terfenadine nor fexofenadine, nor any related piperidine derivatives are naturally produced or known to be suitable as nutritional sources for any of the strains listed in these references. Therefore, it would not be expected that these microorganisms possess or evolve enzymatic pathways capable of performing oxidative transformation of terfenadine or its analogs. Furthermore, biocatalysts are generally known to have a relatively narrow range of specificity for reacting organic compounds (i.e. substrates). Since the carboxylic acids produced by the secondary references (other than Umezawa et al. which does not even have a carboxylic acid as an end product) are structurally distant from terfenadine, one of ordinary skill in the art would have no reason to expect that the microorganisms utilized in these references would be effective in converting terfenadine to fexofenadine.

All microorganisms that are engaged in aerobic metabolism to provide energy and carbon contain oxidative enzymes, and simple carboxylic acids are extremely common reaction products. However, it does not follow that such strains will have activity with terfenadine, let alone cause the addition of two oxygens to the exact desired carbon of the >30 carbons present in the piperidine analogs. Of the secondary references, only Herr et al. describes an oxidative conversion that is distinct from the organism's natural nutritional metabolism. However, this transformation is limited to the introduction of a single hydroxyl group into specific positions of adamantine analogs. Neither the substrates nor the products are chemically similar to the product compounds of the claimed invention.

Since one of ordinary skill in the art would have no reason to combine the teachings of Azerad et al. with those of any of the secondary references, there cannot even be a *prima facie* case of lack of inventive step based on the combination of these references. However, even if, assuming *arguendo,* a *prima facie* case of obviousness was established (which it has not), any *prima facie* case of lack of obviousness is rebutted by the benefits achieved by the claimed invention.

Compared with filamentous bacteria, such as *Streptomyces,* and especially filamentous fungi, such as *Cunninghamella* and *Absidia,* eubacterial strains of the genera *Bacillus* and *Pseudomonas* have several fundamental characteristics that provide many generic advantages for development of efficient commercial processes. For example, filamentous bacteria, such as *Streptomyces,* grow as mycelia in a filamentous morphology, which require specialized fermentation equipment. Even with this specialized equipment, the filamentous morphology increases shear forces and generally decreases maximum mass transfer rates and decreases gas (e.g. oxygen) transport per energy input compared with the homogeneous morphology of non-filamentous bacteria and yeast. Efficiently obtaining high oxygen transport rates is especially important for conducting oxidative biotransformations in which oxygen is a reagent. *Streptomyces* strains also require more complex nutritional requirements resulting in higher medium costs for conducting the reactions. Filamentous growth can also complicate recovery and downstream processing.

For commercial production strategies, which now frequently rely on recombinant strains, simple bacteria such as *Bacillus* and *Pseudomonas* provide several notable advantages compared with *Streptomyces,* and especially filamentous fungi. Organisms containing a high GC content are significantly less suitable as sources for genes encoding potentially useful enzymes. In particular, PCR fidelity (and therefore the ability and convenience to amplify and clone a new gene for a potentially useful synthetic enzyme) is generally much lower for high GC content genes from high GC content genera. In addition, significantly different codon usage by high GC strains makes it more difficult to express their genes in standard expression hosts with low GC content, such as *Escherichia coli.* Finally, high GC strains typically contain substantially more mRNA secondary structure (e.g., helices and loops) that reduce or prevent expression. For example, *Streptomyces* genera have a high GC content in their genomic DNA (i.e. a GC content of 69-78%), especially compared with *Bacillus* (having a GC content of 31.7-40.5%), and other

prokaryotic genera.

Thus, microorganisms used in the claimed process achieve distinct benefits over those used in the prior art to produce piperidine analogs.

For all of the reasons noted above, the obviousness rejection over Azerad et al. in view of the secondary references is respectfully traversed.

35 U.S.C. §101 DOUBLE PATENTING REJECTION

The Examiner rejected claims 1-2, and 25-32 under 35 USC § 101 as allegedly being unpatentable due to being drawn to the same invention as that of issued claim 2 of US 6,613,907.

Without acceding to the propriety of this rejection, and for the purposes of expediting prosecution of the application, Applicants hereby amend scope of R^4 in claim 1. Applicants reserve their right to pursue the original scope of claim 1 in one or more continuation applications. In light of the amendment to claim 1, the 35 USC §101 double patenting rejection is considered moot and its withdrawal is respectfully requested.

NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The Examiner rejected claims 1-2 and 25-32 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 17-32 of US 6,613,907.

Without acceding to the propriety of this rejection, and for the purposes of expediting prosecution of the application, Applicants hereby submit a terminal disclaimer in compliance with 37 CFR 1.321(c). Therefore, the obviousness-type double patenting rejection is rendered moot and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the above remarks and responsive action, reconsideration and further examination is respectfully requested.

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone Edward Timmer, Applicants Attorney at (518) 452-5600 so that such issues may be resolved as expeditiously as possible.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

CERTIFICATE OF MAILING

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Date of Deposit: June 29, 2006

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